

REMARKS

Claims 1-3, 5-13, 15, 19-25, 27, 29-33, 35, 37, and 41-44 are currently pending in this application. Claims 12, 22-24, 42, and 43 remain withdrawn from further consideration as being drawn to a non-elected invention. Claim 13 is objected to for being in improper dependent form. Claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 are rejected under 35 U.S.C. § 112, first paragraph, for new matter, lack of written description, and lack of enablement. Claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 are rejected under 35 U.S.C. § 102(e) for anticipation by Sanberg et al. (U.S. Patent Application Publication No. 2002/0028510 A1; hereinafter “Sanberg”) in view of Rosu-Myles et al. (Stem Cells 18:374-381, 2000; hereinafter “Rosu-Myles”). Finally, the drawings submitted on January 18, 2005, are objected to because they were not labelled “Replacement Sheets.” By this reply, Applicants cancel claims 1-3, 5-13, 15, 19-25, 27, 29-33, 35, 37, and 41-44, add new claims 48-55, and address each of the Examiner’s objections and rejections.

Support for the Amendment

Applicants have cancelled prior claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44, and have added new claims 48-50 in order to clarify the claimed subject matter and to reduce the total number of issues raised in the last Office Action.

Support for new claims 48-50 is found in prior and original claim 1. Support for new claim 51 is found in prior claim 3 and in original claims 32 and 33. Support for new claims 52-55 is found in prior and original claims 7, 10, 11, and 27. No new matter is added by the amendment.

Telephone Interview with the Examiner

Applicants wish to thank the Examiner for the telephonic interview of October 23, 2007.

Applicants regret that consensus as to the patentability of new claims 48-55 was not reached.

Applicants note that only the written description and enablement rejections were discussed.

Applicants believe that present claims 48-55 are in condition for allowance, and respectfully request that the Examiner reconsider her position with respect to the issues discussed during the telephonic interview and the other remaining rejections, which were not discussed during the telephonic interview. If the Examiner believes that present claims 48-55 are not in condition for allowance, Applicants respectfully request that the Examiner contact the undersigned by phone in order to resolve any remaining issues in this case.

Objection to the Drawings

The Examiner objects to the drawings, stating that Figures 1-10 submitted with the reply on January 18, 2005, are not accepted because they were not labeled "Replacement Sheets." In response, Applicants provide drawing sheets 1-10 which have been properly labeled "Replacement Sheets." This objection can now be withdrawn.

Claim Objection

Claim 13 is objected to for being of improper dependent because it does not further limit the subject matter of a previous claim. Applicants have cancelled claim 13. This objection may now be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

New Matter

Claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 are rejected under 35 U.S.C. § 112, first paragraph for new matter. The Examiner states that “the as-filed specification does not contemplate or describe the CD34+/-, Lin- enriched cell fraction as presently recited in the claims.” Applicants have cancelled prior claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44, and new claims 48-55 does not recite this limitation. This rejection can now be withdrawn.

Written Description

Claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 are rejected under 35 U.S.C. § 112, first paragraph, for failing to satisfy the written description requirement. As is discussed above, Applicants have cancelled prior claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 and have added new claims 48-55. Applicants believe that the rejection of prior claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 should not be applied to new claims 48-55 for the reasons discussed below.

In the present Office Action, the Examiner states:

The specification does not further describe “CD34+/-, Lin- cells,” nor does it define the meaning of the designation “CD34+/-”...Given that the specification discloses that the cell composition used in the Example comprises “CD34+/-, Lin- cells,” one of skill in the art would not know the identity of the cell composition that produced the result described therein. Further, given the limited details for obtaining the cell composition used in the Example of the specification, the skilled artisan would not know how to obtain the requisite cell composition for transplantation. This limited information is not deemed sufficient to reasonably

convey to one skilled in the art that Applicants were in possession of the cell compositions required for use in the claimed method, at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed methods of cell transplantation. (Office Action, p. 8.)

Applicants respectfully disagree with the Examiner's basis for this rejection.

As was discussed in the Reply to Office Action filed on January 18, 2005, and during the telephonic interview of October 23, 2007, Applicants explained that the term "CD34+/-, Lin-'" was a shorthand designation chosen by Applicants to more easily identify the population of cells within umbilical cord blood and peripheral blood for use in the recited stroke treatment method. Applicants explained that the designation CD34+/-, Lin- refers to cells that are characterized by the absence of lineage-specific markers (Lin-; i.e., the cells are undifferentiated) and the presence or absence of expression of the cell surface marker CD34 (i.e., CD34+/-). Applicants also explained that instead of referring to these cells using the abbreviated designation "CD34+/-, Lin-'" Applicants could have used a less abbreviated, alternative designation in which this population of cells is described as including both "CD34+, Lin- cells" and "CD34-, Lin- cells."

During the telephonic interview, the Examiner stated that Applicants had provided no evidence to support their position that the population of cells described in the present specification and designated as "CD34+/-, Lin- cells" were the same as, and would be recognized by one skilled in the art as, a population of cells containing both "CD34+, Lin- cells" and "CD34-, Lin- cells." In response, Applicants submit the Declaration of Morey Kraus, which states that the designation "CD34+/-, Lin-'" means, and would be recognized by one skilled in the art as referring to, a population of cells that includes "CD34+, Lin- cells" and "CD34-, Lin-

cells" (see ¶ 3 of the Declaration).¹ Mr. Kraus, who is a co-inventor on the present application, further states that the method described in Example 5 of U.S. Patent No. 5,925,567,² which is incorporated by reference into the present specification as a method for isolating CD34+/-, Lin- cells (see, e.g., page 5, lines 16-18, page 6, lines 21-23, and page 10, lines 9-11), would result in the isolation of a cell population containing both CD34+, Lin- cells and CD34-, Lin- cells (i.e., "CD34+/-, Lin- cells"; see ¶ 4 of the Declaration). Mr. Kraus explains that the negative selection method described in Example 5 of the '567 patent, which utilizes an "[a]ntibody/anti-dextran cocktail composed of the following selection molecules: CD2, CD3, CD14, CD16, CD19, CD24, CD56, CD66b and glycophorin A at concentrations between 0.5 and 1.25 μ g/ μ l each" (col. 17, lines 1-5), produces a population of Lin- cells. Moreover, Mr. Kraus states that although the specification of the '567 patent states that the method produces a population of cells having a "relative increase in CD34+ cells" (i.e., CD34+, Lin- cells; see col. 18, lines 7-10), the negative selection method does not remove CD34- cells that are also Lin- (i.e., CD34-, Lin- cells), and thus, this population of cells would also be included in the population of cells isolated by the method described in Example 5.

Thus, contrary to the Examiner's conclusion, the method disclosed in Example 5 of the '567 patent would result in the preparation of the CD34+/-, Lin- cell population recited in present claims 48-55. Furthermore, as confirmed by Mr. Kraus, Applicants' designation for this population of cells would not be unclear or ambiguous to one of skill in the art, as is discussed above (see ¶ 3 of the Declaration). For all of these reasons, Applicants' specification adequately

¹ Applicants note that the Declaration of Mr. Kraus is being provided unsigned. A signed copy of the Declaration will be provided to the Office.

² Mr. Kraus is also listed as an inventor on the '567 patent.

conveys to one skilled in the art that Applicants, as of the filing date of the application, were in possession of CD34+/-, Lin- cells required for use in the methods of present claims 48-55.

Accordingly, Applicants submit that the written description requirement has been met, and respectfully request that the rejection of claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 under 35 U.S.C. § 112, first paragraph, be withdrawn and not be applied to present claims 48-55.

Enablement

Claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 are also rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states that “the specification does not teach how to use the claimed methods to produce a therapeutic effect nor does it adequately teach how to practice the claimed method, which covers transplantation of a variety of cell types, as well as combined administration of cells and growth factors” (Office Action, p. 10; emphasis in original). Specifically, the Examiner states that the specification fails to provide guidance regarding the cell compositions to be used in transplantation (i.e., the type of cells and the species from which the cells are obtained), and how to obtain a beneficial effect following transplantation (Office Action, p. 9). Applicants respectfully disagree.

The Specification Clearly Discloses
the Isolation of CD34+/-, Lin- Cells
for Treating Stroke

As is discussed above, the specification provides ample guidance and instruction for isolating a population of CD34+/-, Lin- cells for use in the method of present claims 48-55,

using, e.g., the method disclosed in Example 5 of the ‘567 patent, which is incorporated by reference into the present specification. Moreover, Applicants have provided evidence that the designation used in the present specification for this population of cells (i.e., CD34+/-, Lin- cells) would not be unclear or ambiguous to one of skill in the art (see ¶¶ 3 and 4 of the Declaration of Morey Kraus). Thus, Applicants respectfully submit that, contrary to the Examiner’s conclusion, the present specification does enable one of ordinary skill in the art to isolate CD34+/-, Lin- cells for use in the treatment of stroke according to the method of present claims 48-55.

The Specification Clearly Discloses
that the CD34+/-, Lin- Cells of the
Invention are Human Cells

As was discussed during the telephonic interview, Applicants’ specification clearly defines the term “cord blood” as “blood that is derived from the placenta or umbilical cord around the time of the birth of a *human* infant” (see Specification, p. 2, lines 24-25; emphasis added). Thus, the specification confirms that the CD34+/-, Lin- cells from cord blood are *human* cells. Accordingly, Applicants respectfully disagree with the Examiner’s conclusion that the specification fails to disclose the species from which the CD34+/-, Lin- cells of the invention are obtained.

In addition, nothing in the present specification as a whole suggests that CD34+/-, Lin- cells obtained from other sources, such as peripheral blood, should be anything less than human cells, nor does it strain the imagination to believe that Applicants’ reference to methods that involve “administering cells from blood” meant only blood from a human source (see Specification, page 2, lines 22-23). The specification defines “blood” to mean “peripheral, fetal

and cord blood...[but]...not...bone marrow" (see Specification, p. 4, lines 22-23). It would be inconsistent to read the specification as teaching that only cells from cord blood are to be isolated from a human while cells from the other sources of blood are to be isolated from a source other than human. For this reason as well, Applicants respectfully disagree with the Examiner's conclusion that the specification fails to disclose the species from which the CD34+/-, Lin- cells of the invention are obtained.

Finally, Applicants direct the Examiner to ¶ 5 of the Declaration, where Mr. Kraus states that the specification teaches the isolation and use of human CD34+/-, Lin- cells from blood (e.g., cord blood and peripheral blood) to treat conditions such as stroke. Mr. Kraus states that this is plainly described in connection with cord blood on page 2, lines 24-25, of the present specification. Furthermore, Mr. Kraus states that, consistent with the earlier reference in the present specification to cord blood being blood derived from a human infant, the Example described on pages 10-13 of the present specification involved experiments in which *human* CD34+/-, Lin- cells isolated from fresh cord blood were administered to Sprague Dawley rats subjected to middle cerebral artery (MCA) occlusion. For this reason as well, Applicants respectfully disagree with the Examiner's conclusion that the specification fails to disclose the species from which the CD34+/-, Lin- cells of the invention are obtained.

Thus, Applicants respectfully submit that, for all the reasons discussed above, the present specification clearly teaches one of ordinary skill in the art to use human CD34+/-, Lin- cells isolated from cord blood or peripheral blood for use in the method of present claims 48-55. The specification also plainly teaches one skilled in the art how to obtain these cells for use in the method of present claims 48-55. Applicants submit that this basis for the enablement rejection of

prior claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 should be withdrawn and should not be applied to new claims 48-55.

The Specification Clearly Enables the Treatment of Stroke by Administering the CD34+/-, Lin- Cells of the Invention

Finally, and most relevant to the issue of enablement, is whether the present specification teaches one of ordinary skill in the art how to practice the full scope of the method of present claims 48-55 so as to obtain a therapeutic effect. Here, the specification clearly teaches one skilled in the art how to obtain a beneficial effect by administering human CD34+/-, Lin- cells to a human patient according to the method of present claims 48-55.

As evidence, Applicants direct the Examiner to page 10, line 9 through page 13, line 7, of the specification, in which Applicants describe the results of experiments in which Sprague Dawley rats subjected to middle cerebral artery (MCA) occlusion (i.e., a rat stroke model) are treated by direct administration of human CD34+/-, Lin- cells to the site of the stroke. The specification teaches that rats administered 1,000,000 human CD34+/-, Lin- cells by injection directly to the site of the stroke following MCA occlusion showed significant improvement in CNS function as compared to MCA-occluded rats administered vehicle alone; these results were confirmed using two behavioral tests, the forelimb placing test and the hindlimb placing test (see page 10, line 9, through page 13, line 7). Moreover, as is confirmed by Mr. Kraus (see ¶ 5 of the Declaration), the rat MCA-occlusion model described in the present specification is an art-recognized model for treatment in humans, and success in treating stroke using this rat model is predictive of success in treating stroke in humans. Thus, the statistically significant results of

improvement in the MCA-occluded rat model reported in the present specification plainly support the enablement of the method of present claims 48-55 as to the treatment of humans.

Thus, Applicants respectfully submit that the considerable guidance and instruction provided in the present specification would allow one of ordinary skill in the art to isolate human CD34+/-, Lin- cells and to administer these cells directly to the site of stroke so as to achieve an improvement in CNS function. For all of the reasons discussed above, the methods taught in Applicants' specification clearly enable one skilled in the art to practice the full scope of present claims 48-55 without undue experimentation. Moreover, Applicants' evidence of enablement is clearly commensurate in scope with present claims 48-55. Accordingly, Applicants respectfully submit that the rejection of claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 under 35 U.S.C. § 112, first paragraph, should be withdrawn and should not be applied to new claims 48-55.

Rejections under 35 U.S.C. § 102

Claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 are rejected under 35 U.S.C. § 102(e) for anticipation by Sanberg in light of Rosu-Myles. The Examiner states that “Sanberg et al. (2000) disclose a method for treating stroke by administering umbilical cord blood cells...[and that] [t]he disclosure explicitly contemplates using the method of the invention to treat stroke (paragraphs [0042], [0054], [0065], and paragraphs [0161] through [0233]” (Office Action, p. 12). The Examiner further states that “[t]he reference of Sanberg et al. inherently discloses the administration of a cell composition comprising Lin- cells, as recited in the claims, because human cord blood cells inherently comprise Lin- cells, as evidenced by

Rosu-Myles et al.” (Office Action, p. 12). Applicants respectfully disagree.

Applicants have cancelled present claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44, and have added new claims 48-55, which are directed to the treatment of stroke by administering to a patient, directly at the site of a stroke, *isolated* human CD34+/-, Lin- cells from umbilical cord blood (UCB) or peripheral blood. Sanberg fails to teach or suggest the administration of isolated CD34+/-, Lin- cells to a patient for the treatment of stroke.

Sanberg merely describes the treatment of stroke by administering neural cells present in UCB. Sanberg defines “neural cells” as follows:

The term “neural cells” are cells having at least an indication of neuronal or glial phenotype, such as staining for one or more neuronal or glial markers or which will differentiate into cells exhibiting neuronal or glial markers. Examples of neuronal markers which may be used to identify neuronal cells according to the present invention include, for example, neuron-specific nuclear protein, tyrosine hydroxylase, microtubule associated protein, and calbindin, among others. The term neural cells also includes cells which are neural precursor cells, i.e., stem and/or progenitor cells which will differentiate into or become neural cells or cells which will ultimately exhibit neuronal or glial markers, such term including pluripotent stem and/or progenitor cells which ultimately differentiate into neuronal and/or glial cells. (See page 5, paragraph [0053].)

Sanberg discloses that these “neural cells” can be administered in the form of whole UCB, a mononuclear cell fraction of UCB, neural cells isolated from UCB mononuclear cells, neural cells isolated from UCB mononuclear cells and treated with a differentiation agent, or a mononuclear fraction of UCB in which all of the CD34+ cells have been removed (see, e.g., (page 9, [0087], and page 10, [0091]). Nothing in Sanberg teaches or suggests that any of these populations of cells are isolated CD34+/-, Lin- cells or that this population of cells should be administered directly to the site of a stroke in a human patient, as is required by present claims 48-55. Sanberg simply fails to teach or suggest the isolation of Applicants’ population of cells

for use in treating stroke.

In fact, Sanberg teaches away from Applicants' isolated CD34+/-, Lin- cell population by disclosing the use of a cell composition that includes all mononuclear cells from UCB, including, e.g., lineage positive cells, or the use of a cell composition that lacks CD34+ cells, which are present in Applicants' cell population, as is discussed above. Sanberg states that the “[i]nitial experiments with umbilical cord blood utilize all of the mononuclear cells collected without separation of CD34+ cellular components...[while] [o]ther experiments utilize cord blood that is depleted of CD34+ cells” (see, e.g., page 10, paragraph [0091]; emphasis added). Thus, Sanberg not only fails to teach or suggest the use of an isolated population of CD34+/-, Lin- cells for treating stroke, it teaches away from the preparation of this cell population. For this reason as well, Sanberg fails to teach or suggest all of the limitations of present claims 48-55.

Finally, Applicants address the Examiner's reliance on Rosu-Myles to establish the inherent anticipation of claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 based on Sanberg. The Examiner states that Sanberg “inherently discloses administration of a cell composition comprising Lin- cells, as is recited in the claims, because human cord blood cells inherently comprise Lin- cells, as evidenced by Rosu-Myles et al. (Office Action, p. 14). Rosu-Myles, though, fails to remedy the deficiencies of Sanberg. Neither Sanberg nor Rosu-Myles, either alone or in combination, teaches or suggests the use of *isolated* CD34+/-, Lin- cells for treating stroke, as is required by present claims 48-55. Thus, the combination of Sanberg and Rosu-Myles fails to support the inherent anticipation of present claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44.

For all of the reasons given above, Applicants respectfully submit that the rejection of

claims 1-3, 5-11, 13, 15, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 under 35 U.S.C. § 102(e) for anticipation by Sanberg in light of Rosu-Myles should be withdrawn and should not be applied to new claims 48-55.

CONCLUSION

Applicants respectfully submit that present claims 48-55 are in condition for allowance, and respectfully request a notice to that effect.

If there are any additional charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,


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